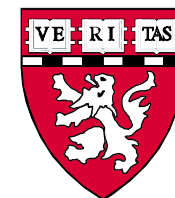

The Landscape of Cure Interventions and Clinical Trials in Adults

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Disclosures

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 - InnaVirVax
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 - ViiV

Some definitions

- **The reservoir**
 - Cells harboring replication-competent provirus that could rekindle HIV-1 replication and/or transmission
- **Latently infected cells**
 - Cells harboring replication-competent provirus in which HIV is transcriptionally silent and in which viral proteins are not expressed
- **Cure**
 - Elimination of all replication-competent viruses and proviruses
- **Remission**
 - A period (TBD) during which ART is not required to maintain a viremia-free state without risk of disease progression, non-AIDS events, or transmission

Background

- **Substantial progress has been made in**
 - Understanding mechanisms of latency
 - Anatomical and cellular nature of the latent reservoir
 - Genetic structure of proviral DNA
 - Contribution of clonal expansion of CD4+ T-cells
 - Development of therapeutic approaches in other disease areas that might be repurposed towards HIV cure

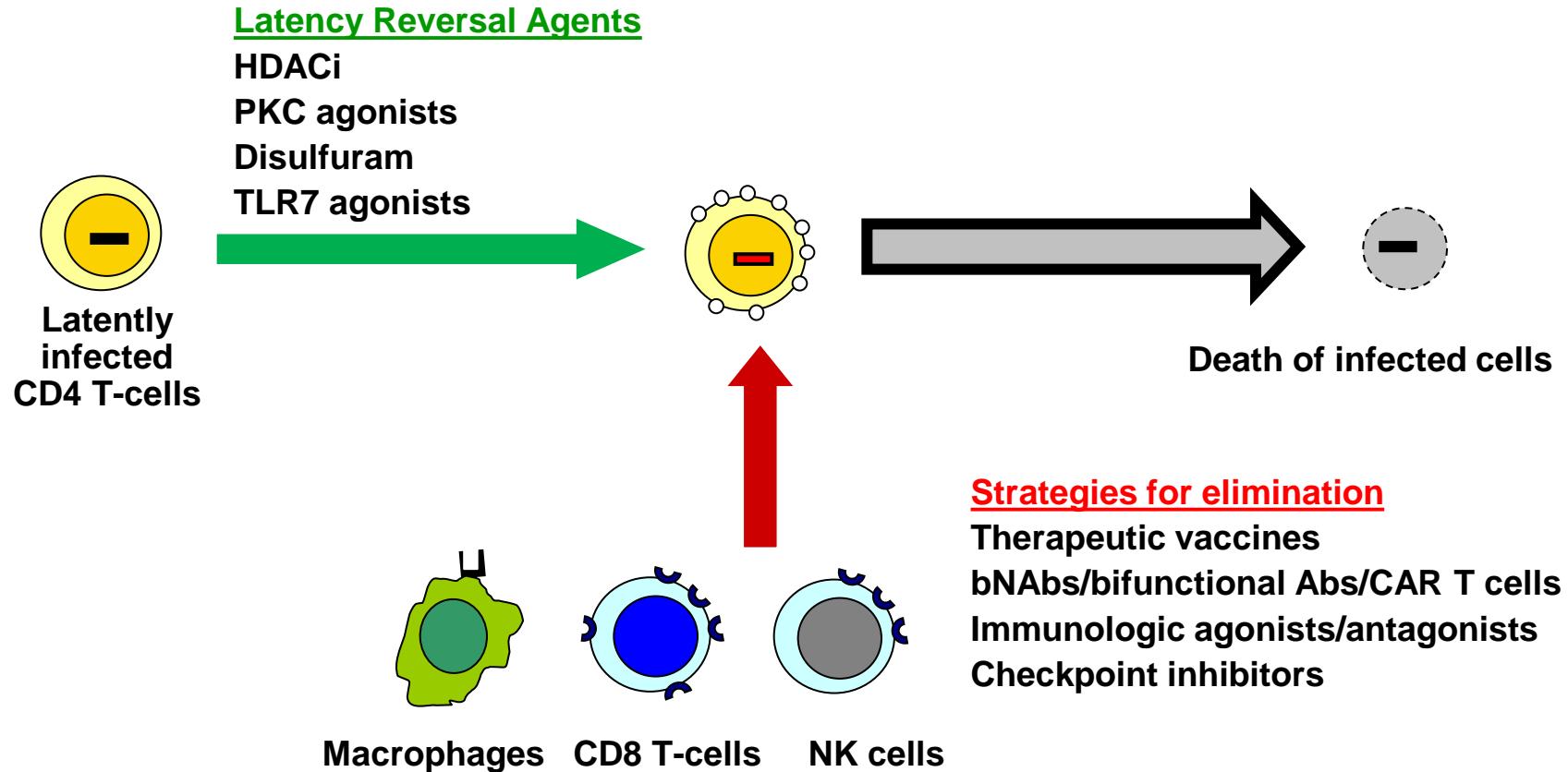
The Central Dogma of HIV Cure

REACTIVATION

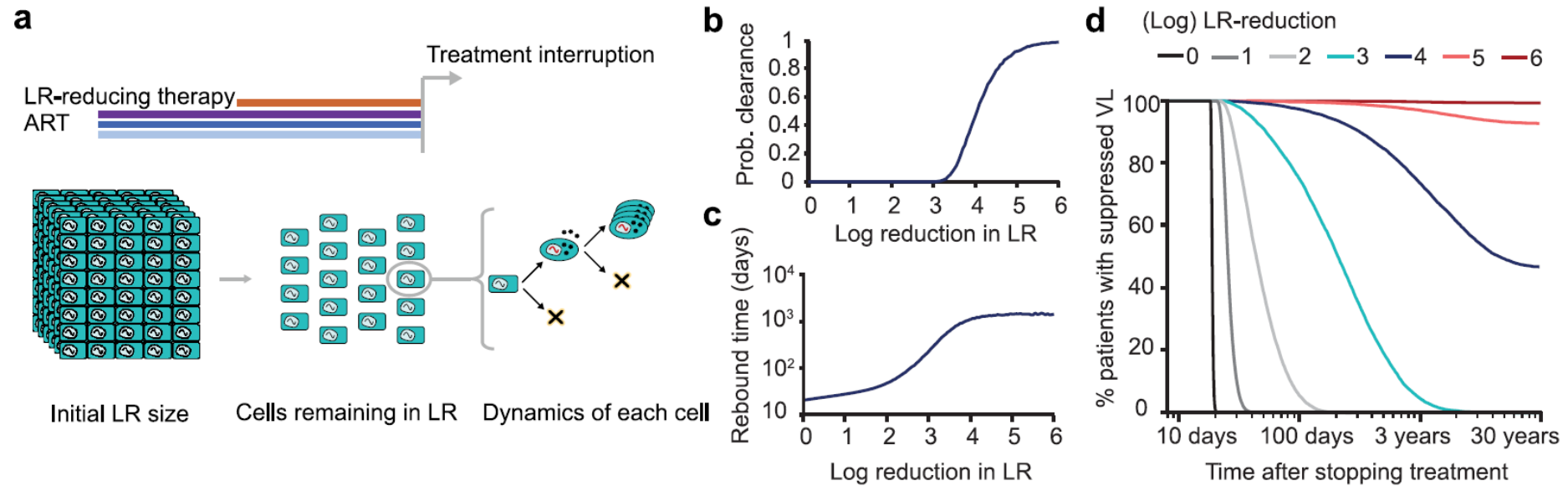
Activate expression of HIV

ELIMINATION

Immune destruction of cells expressing HIV proteins



Model of HIV-1 reservoir dynamics and viral rebound



Approaches to HIV cure

- **Cell-based therapies**

- Autologous transplantation of gene-edited hematopoietic stem cells
- Peripheral CD4+ T cells after gene editing

- **Latency reversal**

- HDAC inhibitors
- TLR agonists

- **Immune-based interventions**

- Check-point inhibitors
- Therapeutic vaccines
- bNAbs/bi-functional Abs/CAR T-cells

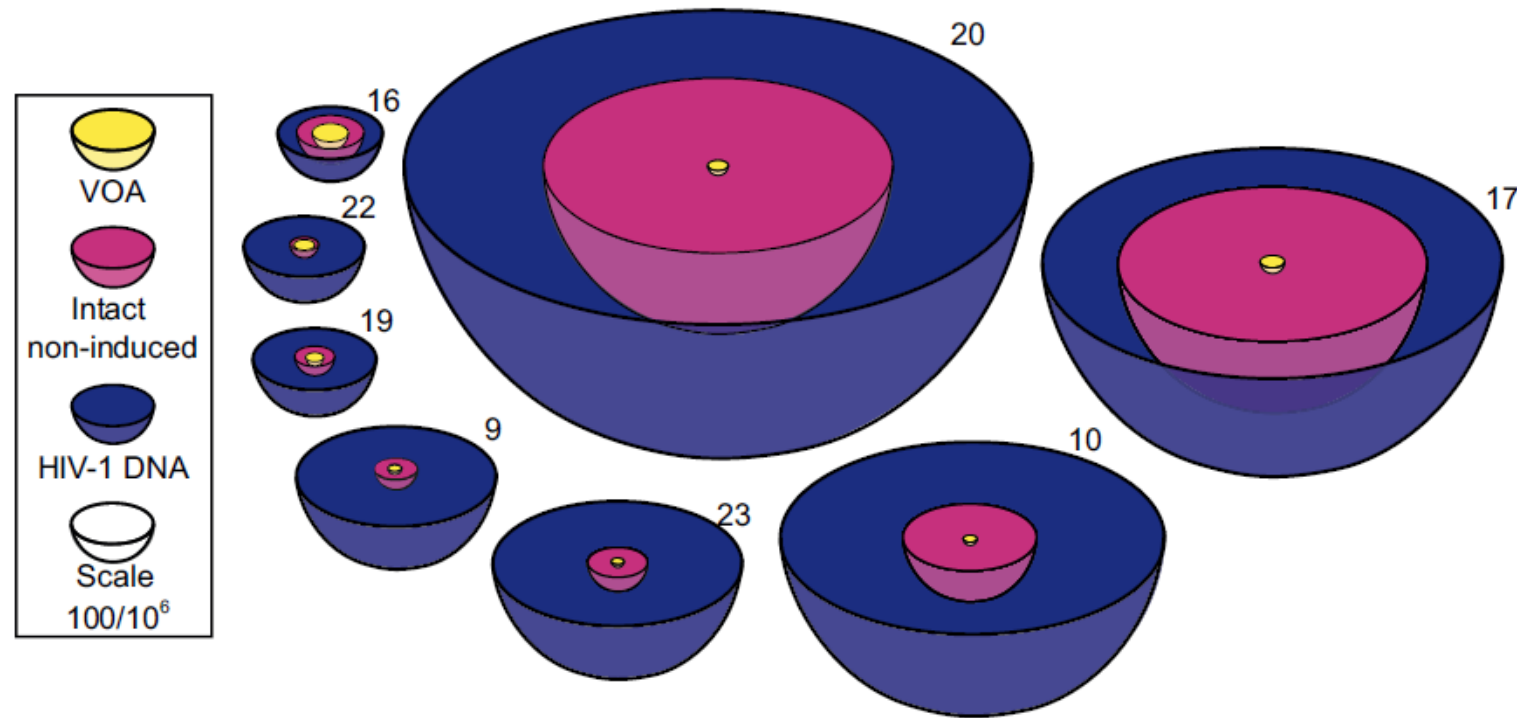
- **Early ART initiation**

- During acute HIV infection
- Early infant (neonatal) treatment

ACTG studies of HIV Cure

- A5308 (ART for elite controllers)
- A5315 (romidepsin)
- A5325 (isotretinoin)
- A5336 (sirolimus)
- A5342 (VRC01)
- **A5345 (treatment interruption)**
- **A5354 (early treatment)**
- **A5366 (vorinostat + tamoxifen)**
- **A5369 (HIV-1 Gag conserved elements therapeutic vaccine)**
- **A5370 (cemiplimab)**
- **A5374 (conserved HIV-1 immunogens therapeutic vaccine)**

Maximal stimulation induces only a fraction of intact HIV-1 proviruses



Why we need surrogate markers in HIV cure research

- Numerous interventions are being investigated as potential approaches to HIV cure/remission
- “Test of cure” ultimately will require analytic treatment interruption (monitored ART pause)
- Prioritization of interventions/combinations to be tested might be simplified by the availability of a validated surrogate marker
- Measuring the relative effects of candidate interventions on a surrogate marker could guide improvements in the approaches

Rethinking treatment interruption

- **ATI is safe if done with appropriate monitoring**
- **Hypothetical risks persist:**
 - Primary infection syndrome
 - Transmission
 - Reseeding of the reservoir
- **Relative merits of time-to-rebound versus change in viral set point as an endpoint**
- **Ethics of ATI in control participants**
 - When is it appropriate to include controls?
 - What if placebos are unavailable?
- **Criteria for resuming ART**

Unanswered questions

- **What is the minimum clinically acceptable duration of drug-free remission?**
- **Are remission/cure sufficient to return the proinflammatory state to normal?**
- **Will remission/cure reduce the risk of non-AIDS clinical events?**
- **How can we determine the effect of remission/ cure on risk of transmission?**
- **At what point can we equate sustained remission to cure?**

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